WEST

Generate Collection Print

154/435, 47, 51
438/710

L3: Entry 8 of 11 File: USPT Aug 15, 2000

DOCUMENT-IDENTIFIER: US 6103033 A
TITLE: Process for producing an electrochemical biosensor

4,512,855

Detailed Description Text (11):
Components are "immobilized" within a sensor, for example, when the components are covalently, ionically, or coordinatively bound to constituents of the sensor and/or are entrapped in a polymeric or sol-gel matrix or membrane which precludes mobility.

Detailed Description Text (21):
Other methods for providing a sample to the sensor include using a pump, syringe, or other mechanism to draw a sample from a patient through tubing or the like either directly to the sensor or into a storage unit from which a sample is obtained for the sensor. The pump, syringe, or other mechanism may operate continuously, periodically, or when desired to obtain a sample for testing. Other useful devices for providing an analyte-containing fluid to the sensor include microfiltration and/or microdialysis devices. In some embodiments, particularly those using a microdialysis device, the analyte may be drawn from the body fluid through a microporous membrane, for example, by osmotic pressure, into a carrier fluid which is then conveyed to the sensor for analysis. Other useful devices for acquiring a sample are those that collect body fluids transported across the skin using techniques, such as reverse iontophoresis, to enhance the transport of fluid containing analyte across the skin.

Detailed Description Text (29):
In some embodiments, the substrate is flexible. For example, if the sensor 42 is configured for implantation into a patient, then the sensor 42 may be made flexible (although rigid sensors may also be used for implantable sensors) to reduce pain to the patient and damage to the tissue caused by the implantation of and/or the wearing of the sensor 42. A flexible substrate 50 often increases the patient's comfort and allows a wider range of activities. A flexible substrate 50 is also useful for an in vitro sensor 42, particularly for ease of manufacturing. Suitable materials for a flexible substrate 50 include, for example, non-conducting plastic or polymeric materials and other non-conducting, flexible, deformable materials. Examples of useful plastic or polymeric materials include thermoplastics such as polycarbonates, polyesters (e.g., Mylar.TM. and polyethylene terephthalate (PET)), polyvinyl chloride (PVC), polyurethanes, polyethers, polyamides, polyimides, or copolymers of these thermoplastics, such as PETG (glycol-modified polyethylene terephthalate).

Detailed Description Text (82):
The sensing layer 64 may be formed as a solid composition of the desired components (e.g., an electron transfer agent and/or a catalyst). These components are preferably non-leachable from the sensor 42 and more preferably are immobilized on the sensor 42. For example, the components may be immobilized on a working electrode 58. Alternatively, the components of the sensing layer 64 may be immobilized within or between one or more membranes or films disposed over the working electrode 58 or the components may be immobilized in a polymeric or sol-gel matrix. Examples of immobilized sensing layers are described in U.S. Pat. Nos. 5,262,035, 5,264,104, 5,264,105, 5,320,725, 5,593,852, and 5,665,222, U.S. patent application No. 08/540,789, and PCT Patent Application No. US96/14534 entitled "Soybean Peroxidase Electrochemical Sensor", filed on Feb. 11, 1998, Attorney Docket No. M&G

12008.8WOI2, incorporated herein by reference.

Detailed Description Text (83):
In some embodiments, one or more of the components of the sensing layer 64 may be solvated, dispersed, or suspended in a fluid within the sensing layer 64, instead of forming a solid composition. The fluid may be provided with the sensor 42 or may be absorbed by the sensor 42 from the analyte-containing fluid. Preferably, the components which are solvated, dispersed, or suspended in this type of sensing layer 64 are non-leachable from the sensing layer. Non-leachability may be accomplished, for example, by providing barriers(e.g., the electrode, substrate, membranes, and/or films) around the sensing layer which prevent the leaching of the components of the sensing layer 64. One example of such a barrier is a microporous membrane or film which allows diffusion of the analyte into the sensing layer 64 to make contact with the components of the sensing layer 64, but reduces or eliminates the diffusion of the sensing layer components (e.g., a electron transfer agent and/or a catalyst) out of the sensing layer 64.

Detailed Description Text (86):
In another embodiment, the sensing layer 64 is not deposited directly on the working electrode 58a. Instead, the sensing layer 64 is spaced apart from the working electrode 58a, as illustrated in FIG. 4A, and separated from the working electrode 58a by a separation layer 61. The separation layer 61 typically includes one or more membranes or films. In addition to separating the working electrode 58a from the sensing layer 64, the separation layer 61 may also act as a mass transport limiting layer or an interferent eliminating layer, as described below.

Detailed Description Text (94):
In many embodiments, the sensing layer 64 contains one or more electron transfer agents in contact with the conductive material 56 of the working electrode 58, as shown in FIGS. 3A and 3B. In some embodiments, it is acceptable for the electron transfer agent to diffuse or leach away from the working electrode, particularly for in vitro sensors 42 that are used only once. Other in vitro sensors may utilize a carrier fluid which contains the electron transfer agent. The analyte is transferred to the carrier fluid from the original sample fluid by, for example, osmotic flow through a microporous membrane or the like.

Detailed Description Text (96):
In some embodiments of the invention, to prevent leaching, the electron transfer agents are bound or otherwise immobilized on the working electrode 58 or between or within one or more membranes or films disposed over the working electrode 58. The electron transfer agent may be immobilized on the working electrode 58 using, for example, a polymeric or sol-gel immobilization technique. Alternatively, the electron transfer agent may be chemically (e.g., ionically, covalently, or coordinatively) bound to the working electrode 58, either directly or indirectly through another molecule, such as a polymer, that is in turn bound to the working electrode 58.

Detailed Description Text (109):
Preferably, the catalyst is non-leachably disposed on the sensor, whether the catalyst is part of a solid sensing layer in the sensor or solvated in a fluid within the sensing layer. More preferably, the catalyst is immobilized within the sensor (e.g., on the electrode and/or within or between a membrane or film) to prevent unwanted leaching of the catalyst away from the working electrode 58 and into the patient. This may be accomplished, for example, by attaching the catalyst to a polymer, cross linking the catalyst with another electron transfer agent (which, as described above, can be polymeric), and/or providing one or more barrier membranes or films with pore sizes smaller than the catalyst.

Detailed Description Text (128):
For proper operation of the temperature probe 66, the temperature-dependent element 72 of the temperature probe 66 can not be shorted by conductive material formed between the two probe leads 68, 70. In addition, to prevent conduction between the two probe leads 68, 70 by ionic species within the body or sample fluid, a covering may be provided over the temperature-dependent element 72, and preferably over the portion of the probe leads 68, 70 that is implanted in the patient. The covering may

be, for example, a non-conducting film disposed over the temperature-dependent element 72 and probe leads 68, 70 to prevent the ionic conduction. Suitable non-conducting films include, for example, Kapton.RTM. polyimide films (DuPont, Wilmington, Del.).

Detailed Description Text (135):
An interferent-eliminating layer (not shown) may be included in the sensor 42. The interferent-eliminating layer may be incorporated in the biocompatible layer 75 or in the mass transport limiting layer 74 (described below) or may be a separate layer. Interferents are molecules or other species that are electroreduced or electrooxidized at the electrode, either directly or via an electron transfer agent, to produce a false signal. In one embodiment, a film or membrane prevents the penetration of one or more interferents into the region around the working electrodes 58. Preferably, this type of interferent-eliminating layer is much less permeable to one or more of the interferents than to the analyte.

Detailed Description Text (141):
Particularly useful materials for the film layer 74 are membranes that do not swell in the analyte-containing fluid that the sensor tests. Suitable membranes include 3 to 20,000 nm diameter pores. Membranes having 5 to 500 nm diameter pores with well-defined, uniform pore sizes and high aspect ratios are preferred. In one embodiment, the aspect ratio of the pores is preferably two or greater and more preferably five or greater.

Detailed Description Text (142):
Well-defined and uniform pores can be made by track etching a polymeric membrane using accelerated electrons, ions, or particles emitted by radioactive nuclei. Most preferred are anisotropic, polymeric, track etched membranes that expand less in the direction perpendicular to the pores than in the direction of the pores when heated. Suitable polymeric membranes included polycarbonate membranes from Poretics (Livermore, Calif., catalog number 19401, 0.01 .mu.m pore size polycarbonate membrane) and Corning Costar Corp. (Cambridge, Mass., Nucleopore.RTM. brand membranes with 0.015 .mu.m pore size). Other polyolefin and polyester films may be used. It is preferred that the permeability of the mass transport limiting membrane changes no more than 4%, preferably, no more than 3%, and, more preferably, no more than 2%, per .degree. C. in the range from 30.degree. C. to 40.degree. C. when the membranes resides in the subcutaneous interstitial fluid.

Detailed Description Text (143):
In some embodiments of the invention, the mass transport limiting layer 74 may also limit the flow of oxygen into the sensor 42. This can improve the stability of sensors 42 that are used in situations where variation in the partial pressure of oxygen causes non-linearity in sensor response. In these embodiments, the mass transport limiting layer 74 restricts oxygen transport by at least 40%, preferably at least 60%, and more preferably at least 80%, than the membrane restricts transport of the analyte. For a given type of polymer, films having a greater density (e.g., a density closer to that of the crystalline polymer) are preferred. Polyesters, such as polyethylene terephthalate, are typically less permeable to oxygen and are, therefore, preferred over polycarbonate membranes.

Detailed Description Text (152):
FIG. 12 is a schematic illustration of an exemplary system 200, in accordance with the principles of the present invention, for manufacturing the sensor 42. The system 200 utilizes a continuous film or substrate web 202 that is guided along a serpentine pathway by a series of rollers 206. Along the pathway, the web 202 is processed at the various processing stations or zones. For example, at one station channels can be formed in the web 202. At subsequent stations, conductive material can be placed in the channels, sensor chemistry can be deposited over portions of the conductive material corresponding with working electrodes, and a protective film or micro-porous membrane can be affixed to the web 202. At a final step, the sensor 42 can be cut, stamped or otherwise removed from the continuous web 202. A more detailed description of the various steps is provided in the following paragraphs.

Detailed Description Text (164):
Silicon is preferred for a flat (non-cylindrical) tool, and may be etched using

techniques common to the integrated circuit industry to create profiles in the wafer surface. Such profiles may be either positive in relief above the surface or negative below the wafer surface. Positive profiles may be used directly as tools to create indentations in a softer substrate. Negative profiles may be used as a master to create a series of second generation positives that are used as the final tool. The second generation positives may be made from any castable material with the appropriate mechanical properties.

Detailed Description Text (184):
Manufacturing Process--Membrane Layer

Detailed Description Text (185):
Upon exiting the heating station 220, the substrate web 202 is brought into alignment with a membrane web 222 adapted for forming a membrane layer, that may include one or more individual membranes, such as a mass transport limiting layer 74 or a biocompatible layer 75, over at least some portions of the electrodes. The membrane layer may be applied to only one or two or more surfaces of the substrate. For certain embodiments, solvents such as methyl ethyl ketone and acetone can be applied, for example, sprayed, on the web 202 to soften the web 202 and solvent bond it to the membrane web 222. By heating the solvent after the web 202 has been brought in contact with the membrane web 222, the two webs 202 and 222 can be bonded together such that the web 222 covers and protects portions of the sensor adapted to be implanted. Alternatively, the two webs 202 and 222 can be bonded or fused together at a welding station 224 such as a sonic or laser welding station. The resultant combination of the substrate web 202 and the membrane web 222 results in a laminated structure in which the protective membrane 74 is selectively fused to the polymer substrate 50. In some embodiments, individual membrane webs 222 are bonded to two or more surfaces of the web 202.

Detailed Description Text (186):
The membrane layer may include one or membranes that individually or in combination serve a number of functions. These include protection of the electrode surface, prevention of leaching of components in the sensing layer, mass transport limitation of the analyte, exclusion of interfering substances, reduction or enhancement of oxygen mass transport, and/or biocompatibility. In one embodiment, a membrane is selected which has mass transport limiting pores that do not change appreciably in size over a physiologically relevant temperature range (e.g., 30.degree. C. to 40.degree. C). This may reduce the temperature dependence of the sensor output.

Detailed Description Text (196):
As a next step in the process, a protective membrane web 328 is then bought into contact with the substrate web 302 such that at least portions of the working and counter electrodes 58 and 60 are covered by the membrane 328. At membrane bonding station 330, the protective membrane 328 and the substrate web 302 are bonded or fused together by techniques such as solvent bonding, adhesive bonding, laser bonding, laser welding, and/or sonic welding. In the case of solvent bonding, the solvent is applied before the protective membrane is brought into contact with the substrate web. A second membrane may optionally be laminated onto the opposing side of the substrate web to protect the reference electrode and temperature probe. The resulting laminate structure that exits the membrane bonding station 330 is conveyed to a cutting station 332 in which individual discrete planforms of the sensor 42" are cut, pressed, stamped or otherwise separated from the continuous web 302. For certain applications, it may be desirable to only partially cut the individual sensor planforms from the web 302 such that the sensors are retained on the web for secondary operations. Remaining web material is taken up by take-up reel 334.

Other Reference Publication (61):
Lindner, E. et al. "Flexible (Kapton-Based) Microsensor Arrays of High Stability for Cardiovascular Applications", J. Chem. Soc.Faraday Trans., 89(2):361-367 (Jan. 21, 1993).

Other Reference Publication (67):
Moatti-Sirat, D. et al., "Reduction of acetaminophen interference in glucose sensors by a composite Nafion membrane: demonstration in rats and man," Diabetologia, 37(6) (1 page--Abstract only) (Jun. 1994).

Other Reference Publication (90):
Sakakida, M. et al., "Ferrocene-mediate needle-type glucose sensor covered with newly designed biocompatible membrane," Sensors and Actuators B, 13-14:319-322 (1993).

Other Reference Publication (100):
Sternberg, R. et al., "Covalent Enzyme Coupling on Celluose Acetate Membranes for Glucose Sensor Development," Analytical Chemistry, 60(24):2781-2786 (Dec. 15, 1988).

Other Reference Publication (125):
Yabuki, S. et al., "Electro-conductive Enzyme Membrane," J. Chem. Soc. Chem. Commun, 945-946 (1989).

Other Reference Publication (128):
Yao, T. et al., "A Chemically-Modified Enzyme Membrane Electrode As An Amperometric Glucose Sensor," Analytica Chimica Acta., 148:27-33 (1983).

CLAIMS:

16. The process of claim 14, wherein the embossing tool is formed of etched silicon, steel, sapphire, epoxy, or ceramic.

38. The process of claim 4, further comprising the step of applying a membrane layer over the two or more electrodes.

39. The process of claim 38, wherein the membrane layer comprises a mass transport limiting layer.

40. The process of claim 38, wherein the membrane layer comprises an interferent eliminating layer.

41. The process of claim 38, wherein the membrane layer comprises a biocompatible layer.

42. The process of claim 38, wherein the membrane layer restricts transport of oxygen to the working electrode.

43. The process of claim 38, wherein said applying a membrane layer comprises applying a micro-porous membrane as a membrane web to the surface of the substrate.

44. The process of claim 38, wherein said applying a membrane layer comprises applying a membrane layer over at least two surfaces of the substrate.

70. The process of claim 4, further comprising the step of bonding a

membrane layer to a surface of the substrate to cover at least one of the two or more electrodes.

79. The process of claim 3, further comprising disposing a membrane layer over the substrate to reduce a temperature dependence of the sensor.